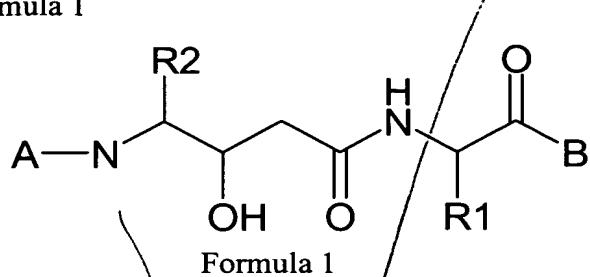


Claims

We claim:

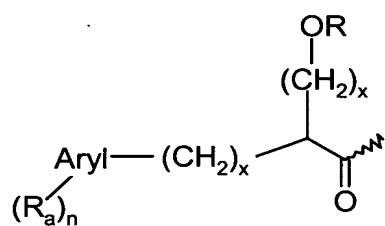
1) A compound of formula 1



wherein:

A is

10 i)



wherein Aryl is mono or bicyclic and has from 5 to 10 ring atoms and may optionally include up to 3 heteroatoms chosen from N, O and S;

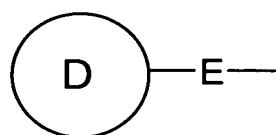
each x is independently 0, 1 or 2;

20 R is H, C₁-C₆ alkyl, phenyl or benzyl wherein each phenyl ring is optionally substituted with up to two groups independently selected from -OH; -CH₂OH, -CO₂H, -CF₃, Cl, Br, F; and C₁-C₂ alkyl;

each R_a is independently selected from the group consisting of H, OH, C₁-C₃ alkyl; C₁-C₆ alkylacylamino, C₁-C₆ alkylacyloxy, C₁-C₆ alkyloxy, C₁-C₆ alkylthioxy, 25 amido (including primary, C₁-C₆ alkyl and phenyl secondary and tertiary), NH₂, mono and di(C₁-C₆ alkyl and phenyl) amino, carbamyl (including C₁-C₆ alkyl and phenyl amides and esters), carboxyl (including C₁-C₆ alkyl and phenyl esters), carboxy(C₂-C₅)alkyloxy and N-heterocyclacyl;

and n is 1 or 2;

30 ii)



wherein D is chosen from aryl having 5 to 6 atoms, optionally including up to 2 heteroatoms selected from the N, O, and S; fused aryl

of 8 to 14 atoms optionally including up to 3 heteroatoms selected from the N, O, and S; mono or fused cycloalkyl having 5 to 12 carbon atoms; and mono or fused heterocycloalkyl having 5 to 12 carbon atoms including up to 3 heteroatoms selected from N, O, and S; biaryl, diaryl ether; diarylketone, and phenyl(C₁-C₈) alkyloxyaryl;

5 and wherein E is a divalent group chosen from carbonyl, sulfonyl, C₁-C₃ alkylene, -X-(C₁-C₃) alkylcarbonyl wherein X is chosen from N, O and S, or E is merely a bond;

and D may optionally be substituted with up to two groups chosen from OH,

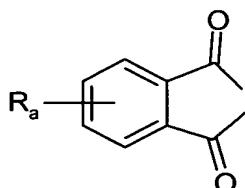
C₁-C₃ alkyl; C₁-C₆ alkylacylamino, C₁-C₆ alkylacyloxy, C₁-C₆ alkyloxy, C₁-C₆ alkylthioxy, amido (including primary, C₁-C₆ alkyl and phenyl secondary and tertiary),

10 NH₂, mono and di(C₁-C₆ alkyl and phenyl) amino, carbamyl (including C₁-C₆ alkyl and phenyl amides and esters), carboxyl (including C₁-C₆ alkyl and phenyl esters), carboxy(C₂-C₅)alkyloxy, N-heterocyclylacyl, C₁-C₃ alkylsulfonyl, sulfonamide and C₁-C₃ alkylsulfonamide;

15 iii) C₁-C₆ alkanoyl; C₂-C₆ alkenoyl; and methylthioC₁-C₅ alkanoyl, any of which may be substituted with up to two groups chosen from OH, C₁-C₆ alkylacylamino, C₁-C₆ alkylacyloxy; C₁-C₆ alkyloxy; C₁-C₆ alkylthioxy, amido (including primary, C₁-C₆ alkyl secondary; C₁-C₆ alkyl and phenyl tertiary, amino, C₁-C₆ alkyl and phenyl amino, carbamyl (including C₁-C₆ alkyl and phenyl amides and esters), carboxyl (including C₁-C₆ alkyl and phenyl esters), carboxy(C₂-C₅)alkyloxy and N-heterocyclylacyl, C₁-C₃ alkylsulfonyl, sulfonamide and C₁-C₃ alkylsulfonamide;

and iv) a divalent group of the formula:

25

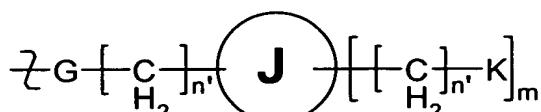


30

wherein each carbonyl of the divalent group bonds to the nitrogen to form a five membered ring and Ra is as defined above;

B is selected from -OH; C₁-C₆ alkyl or C₁-C₆ alkyl amino, di(C₁-C₆ alkyl)amino, C₁-C₆

35 alkyloxy, N-heterocyclylic and



each n' is independently 0, 1 or 2;

m is 0, 1, 2 or 3;

5 and G is N or O;

J is selected from the group consisting of aryl having a 5 to 6 membered ring optionally including up to 2 heteroatoms selected from the N, O, and S; fused aryl rings of 8 to 14 atoms optionally including up to 3 heteroatoms selected from N, O, and S, mono or fused ring cycloalkyl having 5 to 12 carbon atoms; and mono or fused ring heterocyclic having

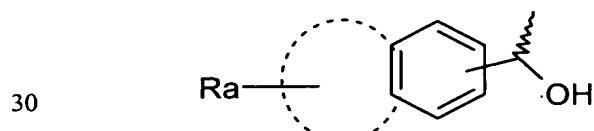
10 5 to 12 carbon atoms including up to 3 heteroatoms chosen from the group consisting of N, O, and S;

each K is chosen from OH, C₁-C₃ alkyl; C₁-C₆ alkylacylamino, C₁-C₆ alkylacyloxy, C₁-C₆ alkyloxy, C₁-C₆ alkylthioxy, amido (including primary, C₁-C₆ alkyl and phenyl secondary 15 and tertiary), NH₂, mono and di(C₁-C₆ alkyl and phenyl) amino, carbamyl (including C₁-C₆ alkyl and phenyl amides and esters), carboxyl (including C₁-C₆ alkyl and phenyl esters) and carboxy(C₂-C₅)alkyloxy;

R1 is straight or branched chain C₁-C₅ alkanyl or C₂-C₅ alkenyl;

20 R2 is C₁₋₅ straight or branched chain alkanyl or alkenyl; methylthiomethyl; aryl or arylalkyl or heteroaryl or heteroarylalkyl wherein any of the above are optionally substituted with up to 2 of C₁₋₃ alkyl, trifluoromethyl or halogen, and stereoisomers, hydrates or pharmaceutically acceptable salts thereof.

25 2) The compound claim 1 wherein A is:



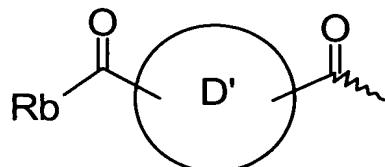
wherein the dotted line indicates an optional aryl ring fused to the phenyl ring.

3) The compound of claim 2 wherein the A is selected from 2-hydroxy-(2-phenyl)ethanoyl, 2-hydroxy-(2-naphth-1-yl)ethanoyl, and 2-hydroxy-(2-naphth-12-yl)ethanoyl.

4) The compound of claim 1 wherein A is selected from biphenyl, 2-phenyl- α -hydroxytolyl, diphenyl ether and diphenyl ketone.

5) The compound of claim 1 wherein A is

5



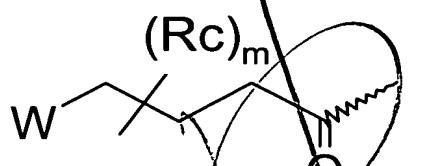
wherein the ring D' is a 5 or 6 membered monocyclic aryl or heteroaryl ring including up

10 to 3 atoms selected from N, O and S, and Rb is $-\text{NH}_2$, mono and di(C₁-C₆ alkyl) amino, C₁-C₆ alkoxy, N-heterocyclic and C₁-C₆ alkyl.

15 6) The compound of claim 5 wherein the ring D' is chosen from the group consisting of benzene, pyridine, furan, thiophene, thiazole, thiadiazole, oxazole, oxadiazole and 1,2,4-triazole and Rb is di(C₂-C₄)alkylamine.

7) The compound of claim 1 wherein A is

20



wherein W is selected from C₁-C₃ alkylthio, C₁-C₃ alkylsulfonyl, primary amido, secondary and tertiary C₁-C₃ alkyl amido, N-heterocyclacyl, primary sulfonamide, secondary and tertiary C₁-C₃ alkyl sulfonamide, and carboxylic acid and C₁-C₃ alkyl esters, Rc may optionally substitute the alkylene chain and is selected from $-\text{OH}$, C₁-C₃ alkyl, Cl and F, and m is 0, 1, 2 or 3.

8) The compound of claim 1 wherein R1 is selected from ethyl and 2-propyl.

30 9) The compound of claim 1 wherein R2 is selected from 2-thienylmethyl, 3-trifluoromethylphenylmethyl, 4-thiazolylmethyl, 3-chlorophenylmethyl, 3,5-difluorophenylmethyl, 4-methylphenylmethyl and 2-methylprop-1-yl.

35 10) The compound of claim 1 wherein R1 is 2-propyl and R2 is 3,5-difluorophenylmethyl.

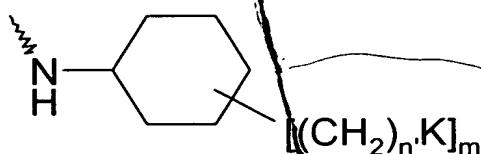
11) The compound of claim 3 wherein R1 is 2-propyl and R2 is 3,5-difluorophenylmethyl.

5 12) The compound of claim 5 wherein R1 is 2-propyl and R2 is 3,5-difluorophenylmethyl.

13) The compound of claim 7 wherein R1 is 2-propyl and R2 is 3,5-difluorophenylmethyl.

10 14) The compound of claim 1 wherein B is -OH, C₁-C₆ alkoxy, mono and di(C₁-C₆) alkylamino, aminoC₁-C₄ alkyl-p-benzoic acid and C₁-C₆ alkyl and phenyl esters thereof and N-heterocyclic.

15) The compound of claim 1 wherein B is



20 wherein K, n' and m are as defined in claim 1.

16) The compound of claim 15 wherein B is selected from 3,5-dicarboxycyclohexylamine, 3,4- dicarboxycyclohexylamine, 3,5- dimethoxycyclohexylamine, 3,5-dihydroxymethylcyclohexylamine and 3,4,5-trimethoxycyclohexylamine.

25 17) The compound of claim 1 wherein A is selected according to claim 2 and B is selected according to claim 14.

30 18) The compound of claim 1 wherein A is selected according to claim 2 and B is selected according to claim 15.

19) The compound of claim 1 wherein A is selected according to claim 5 and B is selected according to claim 14.

20) The compound of claim 1 wherein A is selected according to claim 15 and B is selected according to claim 15.

21) The compound of claim 1 wherein A is selected according to claim 7 and B is selected according to claim 14.

5 22) The compound of claim 1 wherein A is selected according to claim 7 and B is selected according to claim 15.

23) A compound selected from the group consisting of:

10 N -{ N' -[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3S, 4S)-4-amino-3-hydroxy-6-methylheptanoyl} valine (4-carboxy)phenylmethylamide

15 N -{ N' -[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3S, 4S)-4-amino-3-hydroxy-6-methylheptanoyl} valine 2-[(4-carboxy)phenyl]ethylamide

15 N -{ N' -[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3S, 4S)-4-amino-3-hydroxy-6-methylheptanoyl} valine 3-carboxypropylamide

20 N -{ N' -[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3S, 4S)-4-amino-3-hydroxy-6-methylheptanoyl} valine 4-carboxynaphth-1-ylmethylamide

25 N -{ N' -[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3S, 4S)-4-amino-3-hydroxy-6-methylheptanoyl} valine *cis, cis*-3,5-dicarboxycyclohexylamide

30 N -{ N' -[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3S, 4S)-4-amino-3-hydroxy-6-methylheptanoyl} valine 4-carboxycyclohexylamide

35 N -{ N' -[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3S, 4S)-4-amino-3-hydroxy-6-methylheptanoyl} valine

30 N -{ N' -[2-benzyloxy-2-(naphth-1-yl)ethanoyl]-(3S, 4S)-4-amino-3-hydroxy-6-methylheptanoyl} valine (4-carboxy)phenylmethylamide

35 N -[N -(3-hydroxy-2-phenylpropanoyl)-(3S, 4S)-4-amino-3-hydroxy-6-methylheptanoyl] valine (4-carboxy)phenylmethylamide

40 N -{ N' -[2-hydroxy-2-(2-bromophenyl)ethanoyl]-(3S, 4S)-4-amino-3-hydroxy-6-methylheptanoyl} valine (4-carboxy)phenylmethylamide

45 N -{ N' -[2-hydroxy-2-(3-phenoxyphenyl)ethanoyl]-(3S, 4S)-4-amino-3-hydroxy-6-methylheptanoyl} valine (4-carboxy)phenylmethylamide

45 N -{ N' -[(*R*)-2-hydroxy-3-phenylpropanoyl]-(3S, 4S)-4-amino-3-hydroxy-6-methylheptanoyl} valine (4-carboxy)phenylmethylamide

N-[N-(3-hydroxy-3-phenylpropanoyl)-(3S, 4S)-4-amino-3-hydroxy-6-methylheptanoyl]valine (4-carboxy)phenylmethylamide

5 *N-[N-(3, 3, 3-trifluoro-2-methoxy-2-phenylpropanoyl)-(3S, 4S)-4-amino-3-hydroxy-6-methylheptanoyl]valine (4-carboxy)phenylmethylamide*

10 *N-[N'-(R)-2-hydroxy-4-thiomethylbutanoyl)-(3S, 4S)-4-amino-3-hydroxy-6-methylheptanoyl]valine (4-carboxy)phenylmethylamide*

15 *N-[N'-(2-hydroxy-2-phenylethanoyl)-(3S, 4S)-4-amino-3-hydroxy-6-methylheptanoyl]valine (4-carboxy)phenylmethylamide*

20 *N-[N'-(2-hydroxy-2-phenylethanoyl)-(3S, 4S)-4-amino-3-hydroxy-6-methylheptanoyl]valine (4-carboxy)phenylmethylamide*

25 *N-[N'-(2-hydroxy-2-(naphth-1-yl)ethanoyl)-(3S, 4S)-4-amino-3-hydroxy-5-(4-methylphenyl)pentanoyl]valine (4-carboxy)phenylmethylamide*

30 *N-[N'-(2-hydroxy-2-(naphth-1-yl)ethanoyl)-(3S, 4S)-4-amino-3-hydroxy-5-(thien-2-yl)pentanoyl]valine (4-carboxy)phenylmethylamide*

35 *N-[N'-(2-hydroxy-2-(naphth-1-yl)ethanoyl)-(3S, 4S)-4-amino-3-hydroxy-5-(thiazol-4-yl)pentanoyl]valine (4-carboxy)phenylmethylamide*

40 *N-[N'-(3-(N', N'-diethylamido)benzoyl)-(3S, 4S)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine *cis,cis*-3,5-dicarboxycyclohexylamide*

45 *N-[N'-(3-(N'-ethyl-N'-methylamido)benzoyl)-(3S, 4S)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine*

N-[N'-(3-(N'-ethyl-N'-methylamido)benzoyl)-(3S, 4S)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine ethylamide

50 *N-[N'-(3-(N', N'-diethylamido)benzoyl)-(3S, 4S)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine *cis,cis*-3,5-dicarboxycyclohexylamide*

55 *N-[N'-(2-hydroxy-2-(naphth-1-yl)ethanoyl)-(3S, 4S)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine *cis,cis*-3,5-dicarboxycyclohexylamide*

60 *N-[N'-(2-hydroxy-2-(2-phenylphenyl)ethanoyl)-(3S, 4S)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine ethylamide*

65 *N-[N'-(4-N', N'-dimethylamino-5-oxopentanoyl)-(3S, 4S)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine *cis,cis*-3,5-dicarboxycyclohexylamide*

70 *N-[N'-(3-(N'-ethyl-N'-methylamido)benzoyl)-(3S, 4S)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine *cis,cis*-3,5-dimethoxycyclohexylamide*

N-[N'-(benzo-1, 4-dioxan-6-oyl)-(3S, 4S)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine cis,cis-3,5-dicarboxycyclohexylamide

5 *N-[N'-(3-amidobenzoyl)-(3S, 4S)-4-amino-3-hydroxy-5-(3, 5-*

difluorophenyl)pentanoyl]valine cis,cis-3,5-dicarboxycyclohexylamide

10 *N-[N'-(3-(N'-acetylamino)benzoyl)-(3S, 4S)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine cis,cis-3,5-dicarboxycyclohexylamide*

15 *N-[N'-(2-hydroxy-2-(2-methoxyphenyl)ethanoyl)-(3S, 4S)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine cis,cis-3,5-dicarboxycyclohexylamide*

20 *N-[N'-(2-hydroxy-2-(4-methoxyphenyl)ethanoyl)-(3S, 4S)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine cis,cis-3,5-dicarboxycyclohexylamide*

25 *N-[N'-benzoyl-(3S, 4S)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine cis,cis-3,5-dicarboxycyclohexylamide*

30 *N-[N'-(naphth-2-oyl)-(3S, 4S)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine cis,cis-3,5-dicarboxycyclohexylamide*

35 *N-[N'-(3-(N'-methylpiperazido)benzoyl)-(3S, 4S)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine cis,cis-3,5-dicarboxycyclohexylamide*

40 *N-[N'-(2-hydroxy-2-(4-methoxyphenyl)ethanoyl)-(3S, 4S)-4-amino-3-hydroxy-5-(3-trifluoromethylphenyl)pentanoyl]valine cis,cis-3,5-dicarboxycyclohexylamide*

45 *N-[N'-(3-(N", N"-dipropylamido)phenylmethyl)-(3S, 4S)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine cis,cis,cis-3,4,5-trimethoxycyclohexylamide*

50 *N-[N'-(5-(N", N"-dipropylamido)2,6-dimethylpyrid-3-ylcarbonyl)-(3S, 4S)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine cis,cis-3,5-dicarboxycyclohexylamide*

55 *N-[N'-(3-(N", N"-dipropylamido)-2-methoxybenzoyl)-(3S, 4S)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine cis,cis-3,5-dicarboxycyclohexylamide*

60 *N-[N'-(3-(N", N"-dipropylamido)-5-methoxybenzoyl)-(3S, 4S)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine cis,cis-3,5-dicarboxycyclohexylamide*

65 *N-[N'-(3-(2-methylpropionyl)-benzoyl)-(3S, 4S)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine cis,cis-3,5-dicarboxycyclohexylamide*

70 *N-[N'-(5-(N", N"-dipropylamido)-furan-2-ylcarbonyl)-(3S, 4S)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine cis,cis-3,5-dicarboxycyclohexylamide*

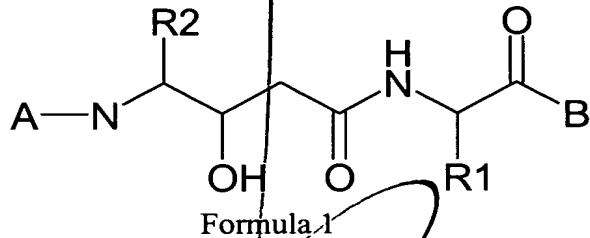
N-{*N*'-[5-(*N*", *N*"-dipropylamido)-thiophen-2-ylcarbonyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide

5 *N*-{*N*'-[5-(*N*", *N*"-dipropylamido)-5-methylbenzoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis,cis*-3,4,5-trimethoxycyclohexylamide

10 *N*-{*N*'-[3-(*N*", *N*"-diethylamido)phenylmethyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide

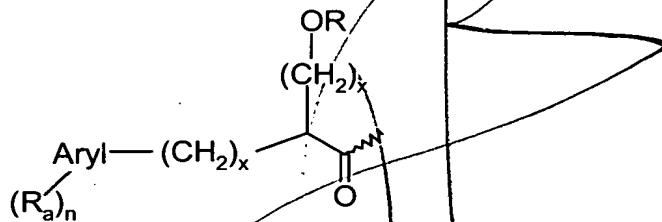
15 *N*-[*N*'-(3-phenylbenzoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine *cis,cis*-3,5-dicarboxycyclohexylamide, and
N-[*N*'-2-pyrimidyl-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine *cis,cis*-3,5-dicarboxycyclohexylamide.

20 24) A method of slowing or ameliorating the progression of a disease state characterized by deposition of A β peptide in a mammal comprising administering to a mammal in need thereof an effective amount of a compound of formula 1



25 wherein:
A is

i)



30 wherein Aryl is mono or bicyclic and has from 5 to 10 ring atoms and may optionally include up to 3 heteroatoms chosen from N, O and S;

each x is independently 0, 1 or 2;

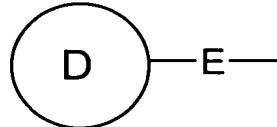
35 R is H, C₁-C₆ alkyl, phenyl or benzyl wherein each phenyl ring is optionally substituted with up to two groups independently selected from -OH; -CH₂OH, -CO₂H, -CF₃, Cl, Br, F; and C₁-C₂ alkyl;

each R_a is independently selected from the group consisting of H, OH, C₁-C₃ alkyl; C₁-C₆ alkylacylamino, C₁-C₆ alkylacyloxy, C₁-C₆ alkyloxy, C₁-C₆ alkylthioxy,

amido (including primary, C₁-C₆ alkyl and phenyl secondary and tertiary), NH₂, mono and di(C₁-C₆ alkyl and phenyl) amino, carbamyl (including C₁-C₆ alkyl and phenyl amides and esters), carboxyl (including C₁-C₆ alkyl and phenyl esters), carboxy(C₂-C₅)alkyloxy and N-heterocyclacyl;

5 and n is 1 or 2;

ii)



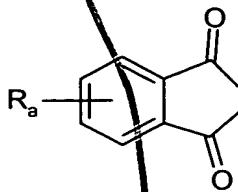
wherein D is chosen from aryl having 5 to 6

10 atoms, optionally including up to 2 heteroatoms selected from the N, O, and S; fused aryl of 8 to 14 atoms optionally including up to 3 heteroatoms selected from the N, O, and S; mono or fused cycloalkyl having 5 to 12 carbon atoms; and mono or fused heterocycloalkyl having 5 to 12 carbon atoms including up to 3 heteroatoms selected from N, O, and S; biaryl, diaryl ether, diarylketone, and phenyl(C₁-C₈) alkyloxyaryl; 15 and wherein E is a divalent group chosen from carbonyl, sulfonyl, C₁-C₃ alkylene, -X- (C₁-C₃) alkylcarbonyl wherein X is chosen from N, O and S, or E is merely a bond; and D may optionally be substituted with up to two groups chosen from OH, C₁-C₃ alkyl; C₁-C₆ alkylacylamino, C₁-C₆ alkylacyloxy, C₁-C₆ alkyloxy, C₁-C₆ alkylthioxy, amido (including primary, C₁-C₆ alkyl and phenyl secondary and tertiary), 20 NH₂, mono and di(C₁-C₆ alkyl and phenyl) amino, carbamyl (including C₁-C₆ alkyl and phenyl amides and esters), carboxyl (including C₁-C₆ alkyl and phenyl esters), carboxy(C₂-C₅)alkyloxy, N-heterocyclacyl, C₁-C₃ alkylsulfonyl, sulfonamide and C₁-C₃ alkylsulfonamide; ..

25 iii) C₁-C₆ alkanoyl; C₂-C₆ alkenoyl; and methylthioC₁-C₅ alkanoyl, any of which may be substituted with up to two groups chosen from OH, C₁-C₆ alkylacylamino, C₁-C₆ alkylacyloxy; C₁-C₆ alkyloxy; C₁-C₆ alkylthioxy, amido (including primary, C₁-C₆ alkyl secondary; C₁-C₆ alkyl and phenyl tertiary, amino, C₁-C₆ alkyl and phenyl amino, carbamyl (including C₁-C₆ alkyl and phenyl amides and esters), carboxyl (including 30 C₁-C₆ alkyl and phenyl esters), carboxy(C₂-C₅)alkyloxy and N-heterocyclacyl, C₁-C₃ alkylsulfonyl, sulfonamide and C₁-C₃ alkylsulfonamide;

and iv) a divalent group of the formula:

5



wherein each carbonyl of the divalent group bonds to the nitrogen to form a five membered ring and R_a is as defined above;

B is selected from -OH; C₁-C₆ alkyl or C₁-C₆ alkyl amino, di(C₁-C₆ alkyl)amino, C₁-C₆ alkyloxy, N-heterocyclic and

15



each n' is independently 0, 1 or 2;

m is 0, 1, 2 or 3;

20 and G is N or O;

J is selected from the group consisting of aryl having a 5 to 6 membered ring optionally including up to 2 heteroatoms selected from the N, O, and S; fused aryl rings of 8 to 14 atoms optionally including up to 3 heteroatoms selected from N, O, and S, mono or fused ring cycloalkyl having 5 to 12 carbon atoms; and mono or fused ring heterocyclic having 25 5 to 12 carbon atoms including up to 3 heteroatoms chosen from the group consisting of N, O, and S;

each K is chosen from OH, C₁-C₃ alkyl; C₁-C₆ alkylacylamino, C₁-C₆ alkylacyloxy, C₁-C₆ alkyloxy, C₁-C₆ alkylthioxy, amido (including primary, C₁-C₆ alkyl and phenyl secondary and tertiary), NH₂, mono and di(C₁-C₆ alkyl and phenyl) amino, carbamyl (including C₁-C₆ alkyl and phenyl amides and esters), carboxyl (including C₁-C₆ alkyl and phenyl esters) and carboxy(C₂-C₅)alkyloxy;

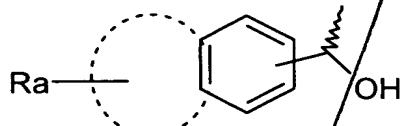
R1 is straight or branched chain C₁-C₅ alkanyl or C₂-C₅ alkenyl;

35

R2 is C₁-5 straight or branched chain alkanyl or alkenyl; methylthiomethyl; aryl or arylalkyl or heteroaryl or heteroarylalkyl wherein any of the above are optionally substituted with up to 2 of C₁-3 alkyl, trifluoromethyl or halogen,

and pharmaceutically acceptable salts and esters thereof.

25) The method claim 24 wherein A is:

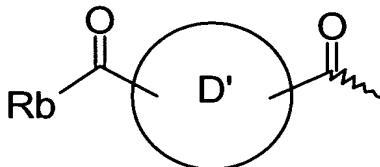


wherein the dotted line indicates an optional aryl ring fused to the phenyl ring.

26) The method of claim 25 wherein the A is selected from 2-hydroxy-(2-phenyl)ethanoyl, 2-hydroxy-(2-naphth-1-yl)ethanoyl, and 2-hydroxy-(2-naphth-12-yl)ethanoyl.

27) The method of claim 24 wherein A is selected from biphenyl, 2-phenyl- α -hydroxytolyl, diphenyl ether and diphenyl ketone.

28) The method of claim 24 wherein A is

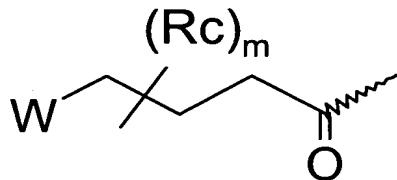


wherein the ring D' is a 5 or 6 membered monocyclic aryl or heteroaryl ring including up to 3 atoms selected from N, O and S, and Rb is $-\text{NH}_2$, mono and di(C₁-C₆ alkyl) amino,

C₁-C₆ alkoxy, N-heterocyclic and C₁-C₆ alkyl.

29) The method of claim 28 wherein the ring D' is chosen from the group consisting of benzene, pyridine, furan, thiophene, thiazole, thiadiazole, oxazole, oxadiazole and 1,2,4-triazole and Rb is di(C₂-C₄)alkylamine.

30) The method of claim 24 wherein A is



wherein W is selected from C₁-C₃ alkylthio, C₁-C₃ alkylsulfonyl, primary amido, secondary and tertiary C₁-C₃ alkyl amido, N-heterocyclacyl, primary sulfonamide, secondary and tertiary C₁-C₃ alkyl sulfonamide, and carboxylic acid and C₁-C₃ alkyl

esters, R_c may optionally substitute the alkylene chain and is selected from $-OH$, C_1-C_3 alkyl, Cl and F , and m is 0, 1, 2 or 3

31) The method of claim 1 wherein R_1 is selected from ethyl and 2-propyl.

5

32) The method of claim 24 wherein R_2 is selected from 2-thienylmethyl, 3-trifluoromethylphenylmethyl, 4-thiazolylmethyl, 3-chlorophenylmethyl, 3,5-difluorophenylmethyl, 4-methylphenylmethyl and 2-methylprop-1-yl.

10

33) The method of claim 24 wherein R_1 is 2-propyl and R_2 is 3,5-difluorophenylmethyl.

34) The method of claim 26 wherein R_1 is 2-propyl and R_2 is 3,5-difluorophenylmethyl.

35) The method of claim 28 wherein R_1 is 2-propyl and R_2 is 3,5-difluorophenylmethyl.

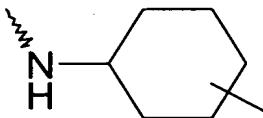
15

36) The method of claim 30 wherein R_1 is 2-propyl and R_2 is 3,5-difluorophenylmethyl.

37) The method of claim 24 wherein B is $-OH$, C_1-C_6 alkoxy, mono and di(C_1-C_6) alkylamino, amino C_1-C_4 alkyl-p-benzoic acid and C_1-C_6 alkyl and phenyl esters thereof and N-heterocyclic.

20

38) The method of claim 1 wherein B is



$[(CH_2)_n.K]_m$

wherein K , n and m are as defined in claim 1.

39) The method of claim 38 wherein B is selected from 3,5-dicarboxycyclohexylamine,

30

3,4-dicarboxycyclohexylamine, 3,5-dimethoxycyclohexylamine,

3,5-dihydroxymethylcyclohexylamine and 3,4,5-trimethoxycyclohexylamine.

40) The method of claim 24 wherein A is selected according to claim 25 and B is selected according to claim 37.

35

41) The method of claim 24 wherein A is selected according to claim 25 and B is selected according to claim 38.

42) The method of claim 24 wherein A is selected according to claim 28 and B is selected according to claim 37.

5 43) The method of claim 24 wherein A is selected according to claim 28 and B is selected according to claim 38.

44) The method of claim 24 wherein A is selected according to claim 30 and B is selected according to claim 37.

10 45) The method of claim 24 wherein A is selected according to claim 30 and B is selected according to claim 38.

46) A method of slowing or ameliorating the progression of a disease state characterized
15 by deposition of A_β peptide in a mammal comprising administering to a mammal in need thereof an effective amount of a compound selected from the group consisting of:

20 *N*-{*N'*-[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine (4-carboxy)phenylmethylamide

25 *N*-{*N'*-[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine 2-[(4-carboxy)phenyl]ethylamide

30 *N*-{*N'*-[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine 3-carboxypropylamide

35 *N*-{*N'*-[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine 4-carboxynaphth-1-ylmethylamide

40 *N*-{*N'*-[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine *cis*,*cis*-3,5-dicarboxycyclohexylamide

45 *N*-{*N'*-[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine 4-carboxycyclohexylamide

50 *N*-{*N'*-[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine

55 *N*-{*N'*-[2-benzyloxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine (4-carboxy)phenylmethylamide

60 *N*-[*N*-(3-hydroxy-2-phenylpropanoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl]valine (4-carboxy)phenylmethylamide

N-{*N*'-[2-hydroxy-2-(2-bromophenyl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine (4-carboxy)phenylmethylamide

5 *N*-{*N*'-[(*S*)-2-hydroxy-3-phenylpropanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine (4-carboxy)phenylmethylamide

10 *N*-{*N*'-[2-hydroxy-2-(3-phenoxyphenyl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine (4-carboxy)phenylmethylamide

15 *N*-{*N*'-[(*R*)-2-hydroxy-3-phenylpropanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine (4-carboxy)phenylmethylamide

20 *N*-[*N*'-(3-hydroxy-3-phenylpropanoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl] valine (4-carboxy)phenylmethylamide

25 *N*-[*N*'-(3, 3, 3-trifluoro-2-methoxy-2-phenylpropanoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl] valine (4-carboxy)phenylmethylamide

30 *N*-{*N*'-[(*R*)-2-hydroxy-4-thiomethylbutanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine (4-carboxy)phenylmethylamide

35 *N*-[*N*'-(2-hydroxy-2-phenylethanoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl] valine (4-carboxy)phenylmethylamide

40 *N*-[*N*'-(2-hydroxy-2-phenylethanoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl] valine (4-carboxy)phenylmethylamide

45 *N*-{*N*'-[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(4-methylphenyl)pentanoyl} valine (4-carboxy)phenylmethylamide

50 *N*-{*N*'-[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(thien-2-yl)pentanoyl} valine (4-carboxy)phenylmethylamide

55 *N*-{*N*'-[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(thiazol-4-yl)pentanoyl} valine (4-carboxy)phenylmethylamide

60 *N*-{*N*'-[3-(*N*', *N*'-diethylamido)benzoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis, cis*-3,5-dicarboxycyclohexylamide

65 *N*-{*N*'-[3-(*N*'-ethyl-*N*'-methylamido)benzoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine

70 *N*-{*N*'-[3-(*N*'-ethyl-*N*'-methylamido)benzoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine ethylamide

75 *N*-{*N*'-[3-(*N*', *N*'-diethylamido)benzoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine

15 *N*-{*N*-[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide

5 *N*-{*N*-[2-hydroxy-2-(2-phenylphenyl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine ethylamide

10 *N*-[*N*-(4-*N*', *N*'-dimethylamino-5-oxopentanoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine *cis,cis*-3,5-dicarboxycyclohexylamide

15 *N*-[*N*-(benzo-1, 4-dioxan-6-oyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine *cis,cis*-3,5-dicarboxycyclohexylamide

20 *N*-[*N*-(3-amidobenzoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine *cis,cis*-3,5-dicarboxycyclohexylamide

25 *N*-{*N*-[3-(*N*'-acetylamino)benzoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine *cis,cis*-3,5-dicarboxycyclohexylamide

30 *N*-{*N*-[2-hydroxy-2-(2-methoxyphenyl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide

35 *N*-{*N*-[2-hydroxy-2-(4-methoxyphenyl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide

40 *N*-[*N*-benzoyl-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine *cis,cis*-3,5-dicarboxycyclohexylamide

45 *N*-[*N*-(naphth-2-oyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine *cis,cis*-3,5-dicarboxycyclohexylamide

N-{*N*-[3-(*N*'-methylpiperazido)benzoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide

50 *N*-{*N*-[2-hydroxy-2-(4-methoxyphenyl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3-trifluoromethylphenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide

55 *N*-{*N*'-[3-(*N*", *N*"-dipropylamido)phenylmethyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis,cis*-3,4,5-trimethoxycyclohexylamide

60 *N*-{*N*-[5-(*N*", *N*"-dipropylamido)2,6-dimethylpyrid-3-ylcarbonyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide

5 *N*-{*N*'-[3-(*N*', *N*"-dipropylamido)-2-methoxybenzoyl]-(*3S*, *4S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide

10 *N*-{*N*'-[3-(*N*', *N*"-dipropylamido)-5-methoxybenzoyl]-(*3S*, *4S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide

15 *N*-{*N*'-[3-(2-methylpropionyl)-benzoyl]-(*3S*, *4S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide

20 *N*-{*N*'-[5-(*N*', *N*"-dipropylamido)-furan-2-ylcarbonyl]-(*3S*, *4S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide

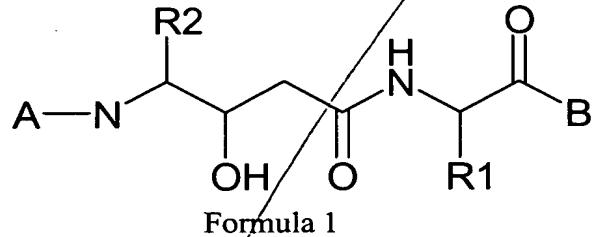
25 *N*-{*N*'-[5-(*N*', *N*"-dipropylamido)-thiophen-2-ylcarbonyl]-(*3S*, *4S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide

30 *N*-{*N*'-[3-(*N*', *N*"-diethylamido)phenylmethyl]-(*3S*, *4S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide

35 *N*-[*N*'-(3-phenylbenzoyl)-(*3S*, *4S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine *cis,cis*-3,5-dicarboxycyclohexylamide, and

40 *N*-[*N*'-2-pyrimidyl-(*3S*, *4S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine *cis,cis*-3,5-dicarboxycyclohexylamide.

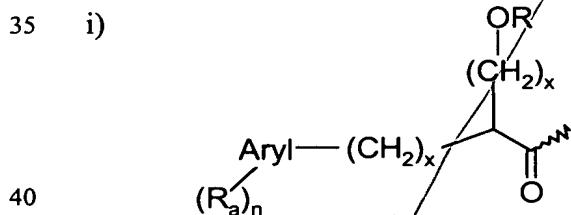
47) A pharmaceutical composition comprising a compound of formula 1



wherein:

A is

35 i)



40 wherein Aryl is mono or bicyclic and has from 5 to 10 ring atoms and may optionally include up to 3 heteroatoms chosen from N, O and S;

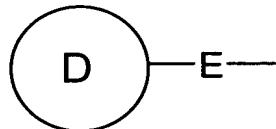
each x is independently 0, 1 or 2;

R is H, C₁-C₆ alkyl, phenyl or benzyl wherein each phenyl ring is optionally substituted with up to two groups independently selected from -OH; -CH₂OH, -CO₂H, -CF₃, Cl, Br, F; and C₁-C₂ alkyl;

5 each R_a is independently selected from the group consisting of H, OH, C₁-C₃ alkyl; C₁-C₆ alkylacylamino, C₁-C₆ alkylacyloxy, C₁-C₆ alkyloxy, C₁-C₆ alkylthioxy, amido (including primary, C₁-C₆ alkyl and phenyl secondary and tertiary), NH₂, mono and di(C₁-C₆ alkyl and phenyl) amino, carbamyl (including C₁-C₆ alkyl and phenyl amides and esters), carboxyl (including C₁-C₆ alkyl and phenyl esters), carboxy(C₂-C₅)alkyloxy and N-heterocyclacylacyl;

10 and n is 1 or 2;

ii)



wherein D is chosen from aryl having 5 to 6 atoms, optionally including up to 2 heteroatoms selected from the N, O, and S; fused aryl of 8 to 14 atoms optionally including up to 3 heteroatoms selected from the N, O, and S; mono or fused cycloalkyl having 5 to 12 carbon atoms; and mono or fused heterocycloalkyl having 5 to 12 carbon atoms including up to 3 heteroatoms selected from N, O, and S; biaryl, diaryl ether; diarylketone, and phenyl(C₁-C₈) alkyloxyaryl; and wherein E is a divalent group chosen from carbonyl, sulfonyl, C₁-C₃ alkylene, -X- (C₁-C₃) alkylcarbonyl wherein X is chosen from N, O and S, or E is merely a bond; and D may optionally be substituted with up to two groups chosen from OH, C₁-C₃ alkyl; C₁-C₆ alkylacylamino, C₁-C₆ alkylacyloxy, C₁-C₆ alkyloxy, C₁-C₆ alkylthioxy, amido (including primary, C₁-C₆ alkyl and phenyl secondary and tertiary), NH₂, mono and di(C₁-C₆ alkyl and phenyl) amino, carbamyl (including C₁-C₆ alkyl and phenyl amides and esters), carboxyl (including C₁-C₆ alkyl and phenyl esters), carboxy(C₂-C₅)alkyloxy, N-heterocyclacyl, C₁-C₃ alkylsulfonyl, sulfonamide and C₁-C₃ alkylsulfonamide;

30

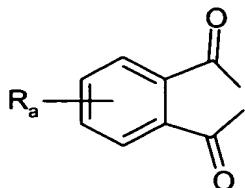
iii) C₁-C₆ alkanoyl; C₂-C₆ alkenoyl; and methylthioC₁-C₅ alkanoyl, any of which may be substituted with up to two groups chosen from OH, C₁-C₆ alkylacylamino, C₁-C₆ alkylacyloxy; C₁-C₆ alkyloxy; C₁-C₆ alkylthioxy, amido (including primary, C₁-C₆ alkyl

secondary; C₁-C₆ alkyl and phenyl tertiary, amino, C₁-C₆ alkyl and phenyl amino, carbamyl (including C₁-C₆ alkyl and phenyl amides and esters), carboxyl (including C₁-C₆ alkyl and phenyl esters), carboxy(C₂-C₅)alkyloxy and N-heterocyclacyl, C₁-C₃ alkylsulfonyl, sulfonamide and C₁-C₃ alkylsulfonamide;

5

and iv) a divalent group of the formula:

10

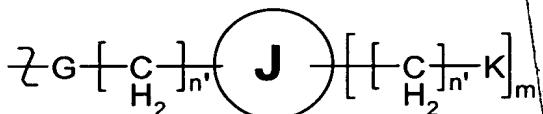


15

wherein each carbonyl of the divalent group bonds to the nitrogen to form a five membered ring and R_a is as defined above;

B is selected from -OH; C₁-C₆ alkyl or C₁-C₆ alkyl amino, di(C₁-C₆ alkyl)amino, C₁-C₆ alkyloxy, N-heterocyclic and

20



each n' is independently 0, 1 or 2;

m is 0, 1, 2 or 3;

25

and G is N or O;

J is selected from the group consisting of aryl having a 5 to 6 membered ring optionally including up to 2 heteroatoms selected from the N, O, and S; fused aryl rings of 8 to 14 atoms optionally including up to 3 heteroatoms selected from N, O, and S, mono or fused ring cycloalkyl having 5 to 12 carbon atoms; and mono or fused ring heterocyclic having 30 5 to 12 carbon atoms including up to 3 heteroatoms chosen from the group consisting of N, O, and S;

35

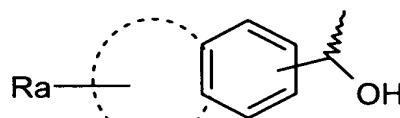
each K is chosen from OH, C₁-C₃ alkyl; C₁-C₆ alkylacyl amino, C₁-C₆ alkylacyloxy, C₁-C₆ alkyloxy, C₁-C₆ alkylthioxy, amido (including primary, C₁-C₆ alkyl and phenyl secondary and tertiary), NH₂, mono and di(C₁-C₆ alkyl and phenyl) amino, carbamyl (including C₁-C₆ alkyl and phenyl amides and esters), carboxyl (including C₁-C₆ alkyl and phenyl esters) and carboxy(C₂-C₅)alkyloxy;

R1 is straight or branched chain C₁-C₅ alkanyl or C₂-C₅ alkenyl;

R2 is C₁₋₅ straight or branched chain alkanyl or alkenyl; methylthiomethyl; aryl or arylalkyl or heteroaryl or heteroaryalkyl wherein any of the above are optionally

5 substituted with up to 2 of C₁₋₃ alkyl, trifluoromethyl or halogen,
and pharmaceutically acceptable salts and esters thereof and a pharmaceutically
acceptable diluent.

48) The composition claim 47 wherein A is:

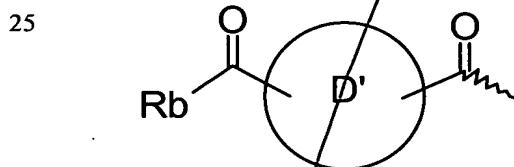


15 wherein the dotted line indicates an optional aryl ring fusion.

49) The composition of claim 48 wherein the A is selected from phenyl)ethanoyl, 2-hydroxy-(2-naphth-1-yl)ethanoyl, aryl)ethanoyl.

20 50) The composition of claim 47 wherein A is selected from hydroxytolyl, diphenyl ether and diphenyl ketone.

51) The composition of claim 47 wherein A is

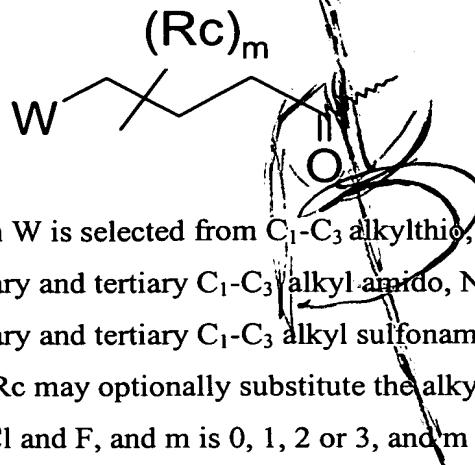


25 wherein the ring D' is a 5 or 6 membered monocyclic aryl or heteroaryl ring including up to 3 atoms selected from N, O and S, and Rb is -NH₂, mono and di(C₁-C₆ alkyl) amino, C₁-C₆ alkoxy, N-heterocyclic and C₁-C₆ alkyl.

52) The composition of claim 51 wherein the ring D' is chosen from the group consisting of benzene, pyridine, furan, thiophene, thiazole, thiadiazole, oxazole, oxadiazole and 1,2,4-triazole and Rb is di(C₂-C₄)alkylamine.

current
version clms
50-52
(5/2/03)

53) The composition of claim 47 wherein A is



5

wherein W is selected from C_1 - C_3 alkylthio, C_1 - C_3 alkylsulfonyl, primary amido, secondary and tertiary C_1 - C_3 alkyl amido, N-heterocyclacyl, primary sulfonamide, secondary and tertiary C_1 - C_3 alkyl sulfonamide, and carboxylic acid and C_1 - C_3 alkyl esters, Rc may optionally substitute the alkylene chain and is selected from -OH, C_1 - C_3 alkyl, Cl and F, and m is 0, 1, 2 or 3, and m is 0, 1, 2 or 3.

10

54) The composition of claim 47 wherein R1 is selected from ethyl and 2-propyl.

15

55) The composition of claim 47 wherein R2 is selected from 2-thienylmethyl, 3-trifluoromethylphenylmethyl, 4-thiazolylmethyl, 3-chlorophenylmethyl, 3,5-difluorophenylmethyl, 4-methylphenylmethyl and 2-methylprop-1-yl.

56) The composition of claim 47 wherein R1 is 2-propyl and R2 is 3,5-difluorophenylmethyl.

20

57) The composition of claim 49 wherein R1 is 2-propyl and R2 is 3,5-difluorophenylmethyl.

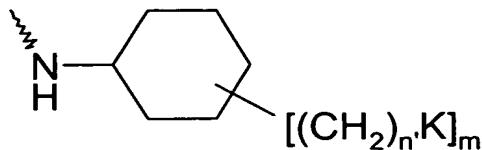
25

58) The composition of claim 51 wherein R1 is 2-propyl and R2 is 3,5-difluorophenylmethyl.

59) The composition of claim 53 wherein R1 is 2-propyl and R2 is 3,5-difluorophenylmethyl.

60) The composition of claim 47 wherein B is -OH, C_1 - C_6 alkoxy, mono and di(C_1 - C_6 alkylamino, amino C_1 - C_4 alkyl-p-benzoic acid and C_1 - C_6 alkyl and phenyl esters thereof and N-heterocyclic.

61) The composition of claim 47 wherein Bis



5

wherein K, n' and m are as defined in claim 1.

62) The composition of claim 61 wherein B is selected from 3,5-dicarboxycyclohexylamine, 3,4- dicarboxycyclohexylamine, 3,5- dimethoxycyclohexylamine,

10 3,5-dihydroxymethylcyclohexylamine and 3,4,5-trimethoxycyclohexylamine.

63) The composition of claim 47 wherein A is selected according to claim 48 and B is selected according to claim 60.

15 64) The composition of claim 47 wherein A is selected according to claim 48 and B is selected according to claim 61.

65) The composition of claim 47 wherein A is selected according to claim 51 and B is selected according to claim 60.

20 66) The composition of claim 47 wherein A is selected according to claim 51 and B is selected according to claim 61.

67) The composition of claim 47 wherein A is selected according to claim 53 and B is selected according to claim 60.

25 68) The composition of claim 47 wherein A is selected according to claim 53 and B is selected according to claim 61.

30 69) A pharmaceutical composition comprising a compound selected from the group consisting of:

N-{N'-[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3S, 4S)-4-amino-3-hydroxy-6-methylheptanoyl} valine (4-carboxy)phenylmethylamide

35

N-{N'-[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3S, 4S)-4-amino-3-hydroxy-6-methylheptanoyl} valine 2-[(4-carboxy)phenyl]ethylamide

N-{*N*'-[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine 3-carboxypropylamide

5 *N*-{*N*'-[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine 4-carboxynaphth-1-ylmethylamide

10 *N*-{*N*'-[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide

15 *N*-{*N*'-[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine 4-carboxycyclohexylamide

20 *N*-{*N*'-[2-hydroxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine

25 *N*-{*N*'-[2-benzyloxy-2-(naphth-1-yl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine (4-carboxy)phenylmethylamide

30 *N*-[*N*'-(3-hydroxy-2-phenylpropanoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl]valine (4-carboxy)phenylmethylamide

35 *N*-{*N*'-[2-hydroxy-2-(2-bromophenyl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine (4-carboxy)phenylmethylamide

40 *N*-{*N*'-[*(S*)-2-hydroxy-3-phenylpropanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine (4-carboxy)phenylmethylamide

45 *N*-{*N*'-[2-hydroxy-2-(3-phenoxyphenyl)ethanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine (4-carboxy)phenylmethylamide

50 *N*-{*N*'-[(*R*)-2-hydroxy-3-phenylpropanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine (4-carboxy)phenylmethylamide

55 *N*-[*N*'-(3-hydroxy-3-phenylpropanoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl]valine (4-carboxy)phenylmethylamide

60 *N*-[*N*'-(3, 3, 3-trifluoro-2-methoxy-2-phenylpropanoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl]valine (4-carboxy)phenylmethylamide

65 *N*-{*N*'-[*(R*)-2-hydroxy-4-thiomethylbutanoyl]-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl} valine (4-carboxy)phenylmethylamide

70 *N*-[*N*'-(2-hydroxy-2-phenylethanoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl]valine (4-carboxy)phenylmethylamide

75 *N*-[*N*'-(2-hydroxy-2-phenylethanoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-6-methylheptanoyl]valine (4-carboxy)phenylmethylamide

N-{*N*'-[(2-hydroxy-2-(naphth-1-yl)ethanoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(4-methylphenyl)pentanoyl} valine (4-carboxy)phenylmethylamide

5 *N*-{*N*'-[(2-hydroxy-2-(naphth-1-yl)ethanoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(thien-2-yl)pentanoyl} valine (4-carboxy)phenylmethylamide

10 *N*-{*N*'-[(2-hydroxy-2-(naphth-1-yl)ethanoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(thiazol-4-yl)pentanoyl} valine (4-carboxy)phenylmethylamide

15 *N*-{*N*'-[3-(*N*', *N*''-diethylamido)benzoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide

20 *N*-{*N*'-[3-(*N*'-ethyl-*N*''-methylamido)benzoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine

25 *N*-{*N*'-[3-(*N*'-ethyl-*N*''-methylamido)benzoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine ethylamide

30 *N*-{*N*'-[3-(*N*', *N*''-diethylamido)benzoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide

35 *N*-{*N*'-[(2-hydroxy-2-(2-phenylphenyl)ethanoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide

40 *N*-[*N*'-(4-*N*', *N*''-dimethylamino-5-oxopentanoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine *cis,cis*-3,5-dimethoxycyclohexylamide

45 *N*-{*N*'-[3-(*N*'-ethyl-*N*''-methylamido)benzoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine *cis,cis*-3,5-dimethoxycyclohexylamide

50 *N*-[*N*'-(benzo-1, 4-dioxan-6-oyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine *cis,cis*-3,5-dicarboxycyclohexylamide

55 *N*-[*N*'-(3-amidobenzoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine *cis,cis*-3,5-dicarboxycyclohexylamide

60 *N*-{*N*'-[3-(*N*'-acetylamino)benzoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide

65 *N*-[*N*'-(3-carbomethoxybenzoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine *cis,cis*-3,5-dicarboxycyclohexylamide

70 *N*-{*N*'-[(2-hydroxy-2-(2-methoxyphenyl)ethanoyl)-(3*S*, 4*S*)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine *cis,cis*-3,5-dicarboxycyclohexylamide

N- {N-[2-hydroxy-2-(4-methoxyphenyl)ethanoyl]-(3S, 4S)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine cis,cis-3,5-dicarboxycyclohexylamide

5 *N-[N'-benzoyl-(3S, 4S)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine cis,cis-3,5-dicarboxycyclohexylamide*

N-[N'-(naphth-2-oyl)-(3S, 4S)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine cis,cis-3,5-dicarboxycyclohexylamide

10 *N- {N-[3-(N'-methylpiperazido)benzoyl]-(3S, 4S)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine cis,cis-3,5-dicarboxycyclohexylamide*

N- {N-[2-hydroxy-2-(4-methoxyphenyl)ethanoyl]-(3S, 4S)-4-amino-3-hydroxy-5-(3-trifluoromethylphenyl)pentanoyl} valine cis,cis-3,5-dicarboxycyclohexylamide

15 *N- {N'-[3-(N", N"-dipropylamido)phenylmethyl]-(3S, 4S)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine cis,cis,cis-3,4,5-trimethoxycyclohexylamide*

N- {N'-[5-(N", N"-dipropylamido)2,6-dimethylpyrid-3-ylcarbonyl]-(3S, 4S)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine cis,cis-3,5-dicarboxycyclohexylamide

20 *N- {N'-[3-(N", N"-dipropylamido)-2-methoxybenzoyl]-(3S, 4S)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine cis,cis-3,5-dicarboxycyclohexylamide*

N- {N'-[3-(N", N"-dipropylamido)-5-methoxybenzoyl]-(3S, 4S)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine cis,cis-3,5-dicarboxycyclohexylamide

25 *N- {N'-[3-(2-methylpropionyl)-benzoyl]-(3S, 4S)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine cis,cis-3,5-dicarboxycyclohexylamide*

30 *N- {N'-[5-(N", N"-dipropylamido)-furan-2-ylcarbonyl]-(3S, 4S)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine cis,cis-3,5-dicarboxycyclohexylamide*

N- {N'-[5-(N", N"-dipropylamido)-thiophen-2-ylcarbonyl]-(3S, 4S)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine cis,cis-3,5-dicarboxycyclohexylamide

35 *N- {N'-[5-(N", N"-dipropylamido)-5-methylbenzoyl]-(3S, 4S)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine cis,cis,cis-3,4,5-trimethoxycyclohexylamide*

N- {N'-[3-(N", N"-diethylamido)phenylmethyl]-(3S, 4S)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl} valine cis,cis-3,5-dicarboxycyclohexylamide

40 *N-[N'-(3-phenylbenzoyl)-(3S, 4S)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine cis,cis-3,5-dicarboxycyclohexylamide ,and*

45 *N-[N'-2-pyrimidyl-(3S, 4S)-4-amino-3-hydroxy-5-(3, 5-difluorophenyl)pentanoyl]valine cis,cis-3,5-dicarboxycyclohexylamide,*

and pharmaceutically acceptable salts and esters thereof, and a pharmaceutically acceptable diluent.

Adel B111